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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NAFF, DAVID M	

ART UNIT	PAPER NUMBER
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/626,459	MIZUNO ET AL.	
	Examiner	Art Unit	
	David M. Naff	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/5/07 has been entered.

An amendment filed 11/5/07 canceled all remaining claims and added new claims 38-48.

Claims examined on the merits are 38-48, which are all claims in the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In claim 38, support is not found in the specification for "cartilage lesions or defects" (bridging lines 1 and 2). The specification discloses defects as lesions, and not defects as an alternative to lesions. It is suggested "or defects" be deleted.

In step f) (lines 9-12 of the step), support is not found in the specification for applying cyclic hydrostatic pressure followed by applying static atmospheric pressure to the matrix of step e) after perfusing as required in step f) (lines 7-8 of the step). According to the specification, applying cyclic hydrostatic pressure followed by applying a static atmospheric pressure occurs during perfusing required in step f). It is suggested line 9 of step f) be amended by before "applying" inserting --- during said perfusing, ---, and canceling "of step e)".

Bridging the last two lines of step f), support is not found in the specification for "said protocol repeated for from about one day to about ninety days". The specification does not disclose repeating a protocol. Additionally, the time of about one day to about ninety days is disclosed in the specification as a time for applying the static atmospheric pressure, and not a time for repeating a protocol. It is suggested "said protocol repeated for from about one day to about ninety days" be deleted.

Support is not found in the specification for the alternatives of "sponge, scaffold, honeycomb or honeycomb-like lattice" as required in line 2 of claim 40. The specification discloses a sponge matrix or honeycomb matrix as being a scaffold, and not a scaffold being an

alternative to a honeycomb or sponge matrix. In line 2, it is suggested "a sponge, scaffold, honeycomb or honeycomb-like lattice" be replaced with --- in the form of a sponge or honeycomb ---.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 38-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The preamble of claim 38 is unclear as to the relationship of providing an implantable construct and providing a means for formation of a superficial cartilage layer to steps a)-h) subsequently required. Defining the method in general terms in the preamble before setting forth specific steps confuses the method performed. It is unclear how the general description of the method in the preamble defines the method in addition to steps a)-h). Additionally, reciting "lesions or defects" (bridging lines 1 and 2) is unclear as to defects that are not lesions since the specification fails to disclose defects that are not lesions. It is suggested the preamble be replaced with --- A method for treatment of cartilage lesions comprising steps: ---.

To be clear, the claim should be further amended as follows.

Line 2 of step a), insert --- stem --- before "cells", and cancel "could" and insert --- can ---.

Line 1 of step b), insert --- stem --- before "cells".

Line 1 of step c) cancel "isolated", and insert --- stem --- before "cells".

Line 2 of step c), after "solution", insert --- to obtain a suspension ---.

Line 1 of step e), cancel "a" and insert --- the ---.

Lines 2 and 4 of step f), insert --- stem --- before "cells".

In lines 7-14 of step f), it is unclear as to when applying cyclic hydrostatic pressure and static atmospheric pressure are applied relative to perfusing. The specification indicates that cyclic hydrostatic pressure and static atmospheric pressure are applied during perfusing, and this should be clear in the claim. It is suggested line line of step f) be amended as set forth above in the 112, first paragraph rejection.

In line 13 of step f), there is not antecedent basis for "said protocol". Additionally, it is uncertain as to steps that would be repeating the protocol since the specification fails to describe repeating a protocol. It is suggested the portion of the step from the comma in line 13 to "days" in line 14 be canceled.

In line 5 of step h), there is not clear antecedent basis in the previous steps for "the superficial". It is suggested the claim recite "a superficial".

In claim 40, "honeycomb-like" is uncertain as to meaning and scope. Being "like" a honeycomb is relative and subjective depending on ones interpretation of material that is like a honeycomb. Claim 40 is further unclear as to a matrix that is a scaffold as an alternative to a sponge, honeycomb and honeycomb-like lattice since the specification fails to describe a scaffold as an alternative as to a sponge, honeycomb and honeycomb-like lattice.

Claim 47 is unclear as to the meaning of "grows into" as an alternative to "provides the same type of". The claim is unclear as to what the cartilage layer grows into, and the specification does not provide any more description than the claim as to what the cartilage layer grows into.

Claim 48 is unclear as to the difference in *in vitro* and *ex vivo* since *in vitro* encompasses *ex vivo* and the converse.

Response to Arguments

In responding to the 112 rejections in the previous office action, the amendment of 11/5/07 canceled previous claims rejected, and added new claims 38-48. While the new claims overcame some of the previous lack of support and indefiniteness, the new claims still do not contain adequate support in the specification and contain indefiniteness for reasons set forth above.

Claim Rejections - 35 USC § 103

Claims 38 and 40-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al (6,528,052 B1) in view of Wise et al

(American Surgeon) and Rhee et al (5,475,052), and if necessary in further view of Rhee et al (5,565,519).

The claims are drawn to a method for treatment of a cartilage lesion or defect by formation of a superficial cartilage layer over an implanted construct comprising activated chondrocytes or stem cells that can be differentiated into chondrocytes. The method is carrier out by isolating chondrocytes or providing stem cells, expanding and suspending the chondrocytes or stem cells in a collagen-containing solution to form a suspension, incorporating the suspension in a support matrix to produce a seeded matrix, preparing an implantable construct for implantation by activating the chondrocytes or stem cells by subjecting the seeded matrix to conditions comprising perfusing the seeded matrix and applying to the seeded matrix cyclic hydrostatic pressure and static atmospheric pressure, implanting the resultant construct in a cartilage lesion, and depositing polyethylene glycol (PEG) cross-linked with methylated collagen over the construct to form within three months a superficial cartilage layer over the implanted construct.

Smith et al disclose regeneration of cartilage tissue in a cartilage defect by seeding a scaffold or support (col 9, line 30) *in vitro* with isolated chondrocytes (col 9, lines 22-33), applying intermittently hydrostatic pressure followed by a recovery period (col 4, lines 37-41 and col 7, line 30 to col 8, line 8) to obtain the scaffold or support containing chondrocytes or cartilage tissue, and

implanting the resultant seeded scaffold or support or cartilage tissue in the cartilage defect (col 9, lines 31-33).

Wise et al disclose using a collagen-polyethylene glycol sealant to seal leaks after liver transplantation.

Rhee et al ('052) disclose using for implant applications a collagen-synthetic polymer matrix that can be a collagen-polyethylene glycol cross-linked matrix (col 16, line 59 and col 24, line 29), and disclose methylated collagen (col 16, line 29) as a chemically modified collagen that can be the collagen of the collagen-synthetic polymer matrix. The chemically modified collagen has an altered charge (col 16, line 26) and is more or less optically clear (col 16, line 32).

Rhee et al ('519) disclose using a collagen-polyethylene glycol conjugate for ophthalmic applications (cols 9-20)

It would have been obvious to seal a defect after implanting cartilage tissue or a scaffold or support seeded with chondrocytes in a defect as disclosed by Smith et al by using a collagen-polyethylene glycol sealant as suggested by Wise et al using this sealant and Rhee et al ('052) using a collagen-polyethylene glycol cross-linked matrix for implant applications. Methylated collagen is taught by Rhee et al ('052) (col 16, line 29) as a modified collagen that can be used as the collagen of the collagen-polyethylene glycol cross-linked matrix for results of altered charge and optically clear collagen, and it would have been obvious to use a methylated collagen-polyethylene glycol cross-linked matrix as the collagen-polyethylene glycol sealant

suggested by Wise et al. It would have been obvious that sealing the defect after implanting will be advantageous to prevent contamination and infection at the site of the defect. The cartilage tissue or seeded scaffold produced by Smith et al before implanting is inherently a construct. If needed, Rhee et al ('519) would have further suggested using a collagen-polyethylene glycol sealant from disclosing using a collagen-polyethylene glycol conjugate for ophthalmic applications. Applying a hydrostatic pressure and static atmospheric pressure as in step f) is suggested by Smith et al disclosing applying intermittent hydrostatic pressure and a recovery period. Perfusing as claimed would have been obvious during culturing to produce cartilage tissue and culture seeded chondrocytes to supply nutrients for cells. The parent application does not antedate Wise et al since the presently claimed invention is not disclosed in the parent application.

Response to Arguments

The amendment of 11/5/07 urges that the gist of the invention is using a polyethylene glycol cross-linked with methylated collagen as a sealant over an implanted construct comprising activated chondrocytes or stem cells to result in overgrowing of the defect with a superficial cartilage layer. However, for reasons set forth above, the references make obvious forming and implanting in a defect a construct as claimed, and after implanting, sealing the defect with a polyethylene glycol cross-linked with methylated collagen. The

formation of a superficial cartilage layer over the defect will be inherent during healing of the defect.

The amendment urges that the superficial cartilage layer is not formed when sealants other than polyethylene glycol cross-linked with methylated collagen are used. However, there is inadequate evidence to support that polyethylene glycol cross-linked with methylated collagen is critical to forming superficial cartilage layer. The specification under the heading "Suitable and Non-suitable Sealants" (page 56) discloses numerous sealants that can be used other than polyethylene glycol cross-linked with methylated collagen. While polyethylene glycol cross-linked with methylated collagen is disclosed as preferred (page 59, lines 18-23), this appears to be because it gels rapidly, and not because it forms a superficial cartilage layer.

The amendment refers to Figure 11 as relating to a control showing production of functionally deficient cartilage tissue. However, it appears the control did not use an implant and sealant for treatment of the defect (paragraph bridging pages 62 and 63 of the specification). The references suggest more than is done with the control, i.e. implanting in a defect cartilage tissue or a seeded scaffold formed as suggested by Smith et al and sealing the defect after implanting with a sealant as suggested as Wise et al. A superficial cartilage layer will inherently form during healing of the defect. Using a sealant would have been obvious to close the wound resulting from surgical implantation against the outside environment for the same reason that a bandage is placed on a wound. Formation of

a superficial cartilage layer will be inherent as the defect heals. Smith et al is not applied alone, but in combination with Wise et al and Rhee et al ('052), and if needed Rhee et al ('519), and these references would have suggested a sealant as claimed.

Double Patenting

Claims 38 and 40-48 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,528,052 B1 in view of Wise et al and Rhee et al (5,475,052), and if necessary in further view of Rhee et al (5,565,519).

For the type of reasons set forth above, it would have been obvious to seal a defect after implanting the in vitro formed cartilage of claim 16 of the patent using a sealant suggested by Wise et al and Rhee et al ('052), and if needed Rhee et al ('519). Formation of a superficial cartilage layer will be inherent when the sealed defect containing the implanted cartilage tissue heals.

Response to Arguments

The type of response set forth above to arguments traversing the 103 rejection also applies to this rejection since the amendment traverses this rejection with the same type of arguments applied to the 103 rejection.

Double Patenting

Claims 38-48 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 7,217,294 in view of Smith et al (6,528,052).

The patent claims require a method of repairing a cartilage lesion by putting a bottom sealant in the lesion, implanting in the lesion a matrix implant, and applying a layer of top sealant over the defect.

It would have been obvious to seed the matrix with chondrocytes *in vitro* before implanting, and apply intermittent hydrostatic pressure and a recovery period as disclosed by Smith et al since the matrix seeded with chondrocytes would have been expected to form new cartilage sooner than using the matrix without the seeded chondrocytes.

Conclusion

Claim 39 is free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is 571-272-0920. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David M. Naff/
Primary Examiner, Art Unit 1657

DMN
2/16/08